PATENT SPECIFICATION

NO DRAWINGS

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833,820

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International Classification:—C07d.

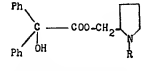
COMPLETE SPECIFICATION

Improvements in or relating to the preparation of Pyrrolidyl Esters and Quaternary Compounds thereof

We, BEECHAM RESEARCH LABORATORIES LIMITED, a British Company, of Brockham Park, Betchworth, Surrey, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the preparation of basic esters and quaternary compounds thereof.

The present invention provides a process for the preparation of compounds of the general formula:



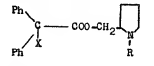
(I)

wherein a 1-alkyl-2-hydroxymethylpyrrolidine of the general formula:

is reacted with an acid halide of the general formula:

(II)

where each X is an atom of chlorine or bromine and R is an alkyl group having from 1 to 4 carbon atoms or an allyl group, to give a compound of the general formula:



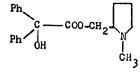
(III)

and the compound of the general formula III is then converted into a compound of the general formula I by treatment with water and a base.

The abbreviation "Ph" is used herein for the phenyl group.

The compounds of the general formula III are new compounds.

The process of the present invention has been found to be particularly suitable for the preparation of compounds of the general formula I where the group R is a methyl or ethyl group. Particularly satisfactory results have been obtained using the process of this invention in the preparation of the compound of the formula:



from 1-methyl-2-hydroxymethylpyrrolidine and α-chloro-diphenylacetyl chloride as described in Example 1 below.

The treatment of the halogen compound of the general formula III with water according to the process of this invention can conveniently be achieved by allowing the halogen compound to stand in water. Where the halogen compound to be treated is (1-methyl-2-pyrrolidyl)-methyl diphenylchloroacetate hydrochloride, it has been found that the corresponding hydroxy compound can be obtained very satisfactorily by dissolving the former compound in water and allowing the resulting solution to stand at room temperature for about 30 minutes.

[*Price 3s. 6d.*]

Price 4s 6d.

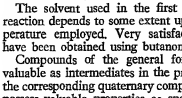
The treatment of compounds of the general formula III with water and with a base according to the process of this invention can, if desired, be carried out simultaneously by using an aqueous solution of the base. However, it is generally preferable to treat the compound of the general formula III first with water to obtain the corresponding hydroxy compound and then to treat the latter with the base. Suitable bases include aqueous solutions of alkalis, for example sodium hydroxide.

The first stage of the process of this invention in which a 1-alkyl-2-hydroxymethylpyrrolidine is reacted with an acid halide in a suitable solvent can be carried out at any convenient temperature. In general this first stage can be performed by mixing the reactants in the solvent and allowing the mixture to stand without the application of external heat. However, if it is wished to complete the reaction in the first stage more quickly, the mixture of reactants can be heated.

The solvent used in the first stage of the reaction depends to some extent upon the temperature employed. Very satisfactory results have been obtained using butanone as solvent.

Compounds of the general formula I are valuable as intermediates in the preparation of the corresponding quaternary compounds which possess valuable properties as spasmolytics.

The present invention, therefore, also includes a process for the preparation of the quaternary compounds, wherein a compound of the general formula I prepared as above defined is reacted with an ester of the general formula R_1Z to form a salt of the general formula:



(IV)

where R is an alkyl group having from 1 to 4 carbon atoms or an allyl group; R_1 is an alkyl group (especially an alkyl group having not more than 4 carbon atoms), or an aralkyl group (for example a benzyl group); and Z is a halogen, alkyl sulphate or aryl sulphonate radical.

Examples of suitable esters include dimethyl sulphate, methyl iodide, ethyl iodide, methyl bromide and ethyl bromide.

If desired the anion Z may be exchanged for any one of the usually accepted anions, for example halide, sulphate, citrate, tartrate, maleate or phosphate, the choice depending to a large extent upon the pharmaceutical convenience and the physical properties which it is desired the salts to possess, for example a particular stability or solubility. Of course, toxic anions, for example the oxalate ion, should be avoided.

The exchange of the anion can be achieved by treating the quaternary compound of the general formula IV with the silver salt of the appropriate acid.

A number of the compounds included in the general formula I are new compounds which have not previously been described and the present invention includes compounds of the general formula I where R is an alkyl group having from 2 to 4 carbon atoms or an allyl group and salts thereof.

The processes of this invention are equally applicable to optically active and optically inactive 1-alkyl-2-hydroxymethylpyrrolidines. The products of this invention are capable of being resolved into optically active isomers and it is to be understood that this invention includes such isomers.

The following Examples illustrate the invention:

EXAMPLE 1.

This Example describes the preparation of *(1-methyl-2-pyrrolidyl)methyl benzilate and its hydrochloride.*

A solution of 1-methyl-2-hydroxymethylpyrrolidine (16 g.) in butanone (40 ml.) was added dropwise while stirring to a solution of α-chlorodiphenylacetyl chloride (39.2 g.) in butanone (80 ml.), care being taken to keep the temperature during the addition below 35° C. The reaction mixture was allowed to stand overnight at 0° C., and after removal of the butanone *in vacuo* the *(1¹-methyl-2¹-pyrrolidyl)methyl 1:1 - diphenyl-1-chloroacetate hydrochloride* was refluxed with dry ether (2 × 120 ml.) and then triturated with dry ether to give the crude hydrochloride (37 g.).

A solution of the (1¹-methyl-2¹-pyrrolidyl)-methyl 1:1-diphenyl-1-chloroacetate hydrochloride (37 g.) in water (700 ml.) was allowed to stand at room temperature for 25 minutes. Sodium chloride (250 g.) was added and the solution extracted with chloroform (6 × 100 ml.). The chloroform extracts were dried using magnesium sulphate and the solvent removed *in vacuo* leaving a gum as the residue. The latter on crystallisation from a mixture of ethanol and ether yielded *(1-methyl-2-pyrrolidyl)methyl benzilate hydrochloride* (29 g.) as colourless needles, m.p. 170—171° C. (Found: C, 66.4; H, 6.7; N, 4.3; Cl, 9.9%. $C_{19}H_{21}O_3NCl$ requires C, 66.4; H, 6.6; N, 3.9; Cl, 9.8%).

Treatment of the hydrochloride (29 g.) dissolved in water with an aqueous solution of sodium hydroxide gave the ester base (24 g.) as colourless needles, m.p. 100—101° C. from light petroleum (b.p. 60—80° C.). (Found: C, 73.9; H, 7.2; N, 4.3%. $C_{19}H_{21}O_3N$ requires C, 73.8; H, 7.1; N, 4.3%).

The 1-methyl-2-hydroxymethylpyrrolidine used in the process described above was obtained as a colourless liquid, b.p. 57—58° C./4 mm. $n_D^{19.6}$ 1.4692 by the formaldehyde-formic acid methylation of 2-hydroxymethyl-

pyrrolidine. The latter was prepared by the reduction with lithium aluminium hydride of butyl pyroglutamate, derived from L-glutamic acid (cf. Karrer and Portman, *Helv. Chim. Acta.*, 1948, *31*, 2088. Blicke and Lu, *J. Amer. Chem. Soc.*, 1955, *77*, 29). It was obtained in 62% yield as a colourless liquid, b.p. 89° C./6 mm. n_D^{25} 1.4846.

The 1-methyl-2-hydroxymethylpyrrolidine prepared as described in our co-pending Application No. 21193/56 (Serial No. 820,503) can be used similarly.

EXAMPLE 2.

This Example describes the preparation of *(1-methyl-2-pyrrolidyl)methyl benzilate methiodide.*

(1-Methyl-2-pyrrolidyl)methyl benzilate (12.2 g.), obtained as described in Example 1, was dissolved in dry benzene (50 ml.) and to the solution was added methyl iodide (7.5 ml.). The reaction mixture became turbid and was allowed to stand at room temperature for 20 hrs. after which the benzene layer was decanted and the gum remaining was washed with dry ether, triturated with dry ethanol and allowed to stand overnight at 0° C. The product obtained was the crude *methiodide* (17 g. 97%) which, after being crystallised from ethyl acetate-methanol/ether, was obtained as colourless microprisms, m.p. 192° C. (Found: C, 53.8; H, 5.7; I, 26.8%. $C_{21}H_{26}O_3NI$ requires C, 54.0; H, 5.6; I, 27.2%).

EXAMPLE 3.

This Example describes the preparation of *(1-methyl - 2 - pyrrolidyl)methyl benzilate ethiodide.*

(1-Methyl-2-pyrrolidyl)methyl benzilate (2 g.) (see Example 1) in benzene (10 ml.) was treated with ethyl iodide (1.5 ml.) using the method described in Example 2, to give the *ethiodide* (1.2 g. 40%) which crystallised from ethyl acetate-methanol/ether as colourless needles, m.p. 146—148° C. (Found C, 54.7; H, 5.6; I, 26.0%. $C_{22}H_{28}O_3NI$ requires C, 54.9; H, 5.8; I, 26.4%).

An identical product may be obtained by the reaction of (1-ethyl-2-pyrrolidyl)methyl benzilate (Example 6) with methyl iodide.

EXAMPLE 4.

This Example describes the preparation of *(1-methyl - 2 - pyrrolidyl)methyl benzilate methobromide.*

(1-Methyl-2-pyrrolidyl)methyl benzilate (2 g.) (see Example 1) in benzene (10 ml.) was treated with methyl bromide (1.4 ml.) as described in Example 2 to give the methobromide (3.5 g.), m.p. 171° C. as colourless needles from acetone. (Found: C, 60.5; H, 6.6; Br, 19.4%. $C_{21}H_{26}O_3NBr$ requires C, 60.0; H, 62; Br, 19.0%).

EXAMPLE 5.

This Example describes the preparation of *(1 - methyl - 2 - pyrrolidyl)methyl benzilate methyl methosulphate.*

(1-Methyl-2-pyrrolidyl)methyl benzilate (325 g.) prepared as described in Example 1 was dissolved in warm dry acetone (1200 ml.) and dimethyl sulphate (158 g.) was added. After the initial exothermic reaction was complete the mixture was refluxed for 15 minutes and then cooled. The precipitated *(1-methyl-2-pyrrolidyl)methyl benzilate methyl methosulphate* obtained (384 g. 85%), m.p. 135—137° C., was removed by filtration and could be recrystallised from a mixture of 10% ethanol in butanone.

The (1-methyl-2-pyrrolidyl)methyl benzilate used in the preparation described in this Example had been prepared from 1-methyl-2-hydroxymethyl pyrrolidine obtained as described in our specification No. 21193/56 (Serial No. 820,503).

EXAMPLE 6.

This Example describes the preparation of *(1 - ethyl - 2 - pyrrolidyl)methyl benzilate hydrochloride.*

Reaction of α-chlorodiphenylacetyl chloride (11.5 g.) in butanone (5 ml.) with a solution of 1-ethyl-2-hydroxymethyl pyrrolidine (3.6 g.) in butanone (5 ml.) as in Example 1 gave *(1-ethyl - 2¹ - pyrrolidyl)methyl - 1:1 -diphenyl-1-chloroacetate hydrochloride* (13 g.).

Hydrolysis of the chloroacetate with water as described in Example 1 gave *(1-ethyl-2-pyrrolidyl)methyl benzilate hydrochloride* (70%) obtained as colourless needles from ethyl acetate-butanone, m.p. 144—145° C. (Found: C, 67.2; H, 7.0; Cl, 9.5%. $C_{21}H_{25}O_3NCl$ requires C, 67.1; H, 6.9; Cl, 9.5%).

The parent alcohol, *1-ethyl-2-hydroxymethylpyrrolidine*, was obtained as follows:—2-Hydroxymethylpyrrolidine was refluxed with acetic anhydride to give *(1-acetyl-2-pyrrolidyl) methyl acetate* (52%) as colourless needles, m.p. 46—47° C., on crystallisation from light petroleum (b.p. 80—100° C.). The diacetate on reduction with lithium aluminium hydride in ether gave *1-ethyl-2-hydroxymethylpyrrolidine* (75%) as a colourless liquid, b.p. 76° C./13 mm. n_D^{18} 1.4720.

The same alcohol can also be obtained by the process of our co-pending Application No. 21193/56 (Serial No. 820,503).

EXAMPLE 7.

This Example describes the preparation of *(1-n-propyl-2-pyrrolidyl)methyl benzilate hydrochloride.*

Reaction of α-chlorodiphenylacetyl chloride (9 g.) with 1-*n*-propyl-2-hydroxymethyl-pyrrolidine (4.2 g.) in butanone (10 ml.) at room temperature for 17 hrs. as in Example 1 gave *(1'-n-propyl-2¹-pyrrolidyl)methyl-1:1-diphenyl-1'-chloroacetate hydrochloride* (11.52 g. 82%).

The latter (5 g.) was converted as described in Example 1 to give *(1-n-propyl-2-pyrrolidyl)methyl benzilate hydrochloride* (3.6 g. 73%) as colourless needles, m.p. 159—160° C. from butanone. (Found: C, 67.8; H, 7.2;

Cl, 9.1%. $C_{23}H_{28}O_3NCl$ requires C, 67.8; H, 7.1; Cl, 9.1%).

The parent alcohol, *1-n-propyl-2-hydroxymethylpyrrolidine* was prepared as follows:—The action of propionic anhydride on 2-hydroxymethylpyrrolidine yielded *(1-propionyl - 2 - pyrrolidyl)methyl propionate* (71%) as a colourless liquid, b.p. 112—113° C./0.015 mm. n_D^{20} 1.4720. The latter on reduction with lithium aluminium hydride was then converted into *1-n-propyl-2-hydroxymethylpyrrolidine* (41%) which was obtained as a colourless liquid, b.p. 44° C./0.05 mm. n_D^{22} 1.4659.

The same alcohol can also be obtained by the process of our co-pending Application No. 21193/56 (Serial No. 820,503).

EXAMPLE 8.

This Example describes the preparation of *(1-iso-propyl-2-pyrrolidyl)methyl benzilate hydrochloride*.

1-*iso*-Propyl-2-hydroxymethyl pyrrolidine (3.7 g.) was allowed to react with α-chlorodiphenylacetyl chloride (6.8 g.) as described in Example 1 to give *(1¹-iso-propyl-2¹-pyrrolidyl)methyl - 1:1 - diphenyl - 1 - chloroacetate hydrochloride* as a gum. This was treated with water as described in Example 1, to give *(1-iso-propyl-2-pyrrolidyl) methyl benzilate hydrochloride* (7.3 g. 72%) as colourless needles from butanone-ethanol, m.p. 165—166° C. (Found: C, 67.5; H, 7.1; Cl, 9.2%. $C_{23}H_{28}O_3NCl$ requires C, 67.8; H, 7.2; Cl, 9.1%).

The parent alcohol, *1-iso-2-hydroxymethylpyrrolidine* was prepared by reacting *iso*-propyl iodide with the potassium derivative of butyl pyroglutamate when *butyl-1-iso-propyl pyroglutamate* (41%) was obtained as a colourless liquid, b.p. 116—117° C./0.05 mm. n_D^{19} 1.4621. Reduction of the latter using lithium aluminium hydride then yielded *1-iso-propyl-2-hydroxymethylpyrrolidine* (41%), b.p. 54—56° C./0.02 mm. n_D^{21} 1.4721.

The same alcohol can also be obtained by the method of our co-pending Application No. 21193/56 (Serial No. 820,503).

EXAMPLE 9.

This Example describes the preparation of *(1-iso-propyl-2-pyrrolidyl)methyl benzilate methiodide methosulphate*.

1-*iso*-Propyl-2-pyrrolidylmethyl benzilate hydrochloride prepared as described in Example 1 was converted to the oily free base as described in Example 1 and this (10 g.) converted to the methyl methosulphate (7.5 g. 55%) m.p. 165—167° C., as described in Example 4.

EXAMPLE 10.

This Example describes the preparation of *(1-n-butyl - 2 - pyrrolidyl)methyl benzilate hydrochloride*.

A solution of 1-*n*-butyl-2-hydroxymethylpyrrolidine (5.9 g.) in butanone (10 ml.) was allowed to react with a solution of α-chlorodiphenylacetyl chloride (10 g.) in butanone (10 ml.) as described in Example 1, to give *(1¹-n - butyl - 2¹ - pyrrolidyl)methyl - 1:1 - diphenyl - 1 - chloroacetate hydrochloride* (913.2 g. 83%).

The latter (4 g.) was then converted as described in Example 1, to give *(1-n-butyl-2-pyrrolidyl)methyl benzilate hydrochloride* (2.6 g. 68%) as colourless needles, m.p. 171—172° C. from butanone-ethanol. (Found C, 68.3; H, 7.2; Cl, 8.6%. $C_{25}H_{30}O_3NCl$ requires C, 68.7; H, 7.5; Cl, 8.8%).

The parent alcohol, *1-n-butyl-2-hydroxymethylpyrrolidine* was obtained as follows:—Refluxing 2-hydroxymethylpyrrolidine with butyric anhydride gave *(1-butyryl-2-pyrrolidyl)methyl butyrate* (87%) as a colourless liquid, b.p. 113° C./0.05 mm. n_D^{24} 1.4672. The latter on reduction with lithium aluminium hydride was converted into *1-butyl-2-hydroxymethylpyrrolidine* (87%) as a colourless liquid, b.p. 61° C./0.4 mm. n_D^{23} 1.4638.

The same alcohol can also be obtained by the method of our co-pending Application No. 21193/56 (Serial No. 820,503).

EXAMPLE 11.

This Example describes the preparation of *(1-allyl-2-pyrrolidyl)methyl benzilate hydrochloride*.

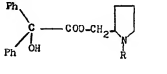
A solution of 1-allyl-2-hydroxymethylpyrrolidine (15 g.) in butanone (20 ml.) was allowed to react with α-chlorodiphenylacetyl chloride (28 g.) in butanone (25 ml.) as described in Example 1, to give *(1¹-allyl-2¹-pyrrolidyl)-methyl-1:1-diphenyl - 1 - chloroacetate hydrochloride* (30 g. 70%).

The latter (5 g.) was then converted as described in Example 1 to give *(1-allyl-2-pyrrolidyl)methyl benzilate hydrochloride* (2.8 g. 60%) as colourless plates, m.p. 128—130° C., from butanone/ether. (Found: C, 68.2; H, 6.9; Cl, 9.2%. $C_{23}H_{26}O_3NCl$ requires C, 68.3; H, 6.7; Cl, 19.2%).

The parent alcohol, *1-allyl-2-hydroxymethyl pyrrolidine*, was obtained as follows: The reaction of the potassio derivative of butyl pyroglutamate with allyl bromide gave *butyl-1-allyl-pyroglutamate* (49%), b.p. 112° C./0.05 mm. n_D^{25} 1.4771. The latter on reduction with lithium aluminium hydride gave *1-allyl-2-hydroxymethylpyrrolidine* (71%) as a colourless liquid, b.p. 86° C./10 mm. n_D^{25} 1.4829.

WHAT WE CLAIM IS:—

1. A process for the preparation of compounds of the general formula



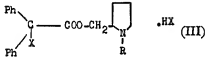
(I)

wherein a 1-alkyl-2-hydroxymethylpyrrolidine of the general formula

is reacted with an acid halide of the general formula

(II)

where X is an atom of chlorine or bromine and R is an alkyl group having from 1 to 4 carbon atoms or an allyl group, to give a compound of the general formula

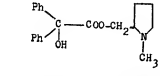


(III)

and the compound of the general formula III is then converted into a compound of the general formula I by treatment with water and a base.

2. A process as claimed in claim 1 wherein the group R is a methyl or ethyl group.

3. A process for the preparation of a compound of the general formula

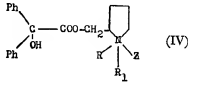


wherein 1-methyl-2-hydroxymethylpyrrolidine is reacted with α-chlorodiphenylacetyl chloride and the resulting product is treated with water and a base.

4. A process as claimed in any one of the preceding claims wherein the treatment of the compound of the general formula III with water is achieved by allowing the compound to stand in water at room temperature.

5. A process as claimed in any one of the preceding claims wherein the base is an aqueous solution of an alkali.

6. A process as claimed in any one of the preceding claims wherein the compound of the general formula I is reacted with an ester of the general formula R_1Z to form a salt of the general formula



(IV)

where R is an alkyl group having from 1 to 4 carbon atoms or an allyl group, R_1 is an alkyl group or an aralkyl group and Z is a halogen, alkyl sulphate or aryl sulphonate radical.

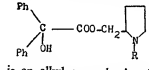
7. A process as claimed in claim 6 wherein the ester is dimethyl sulphate.

8. A process as claimed in claim 6 wherein the ester is methyl iodide, ethyl iodide, methyl bromide or ethyl bromide.

9. A process as claimed in any one of claims 6 to 8 wherein the anion Z in the compound of general formula IV specified in claim 6 is exchanged for another non-toxic anion.

10. A process as claimed in claim 9 wherein the exchange of anions is effected by treating the compound of the general formula IV with the silver salt of the appropriate acid.

11. Compounds of the general formula:



where R is an alkyl group having from 2 to 4 carbon atoms, or an allyl group, and salts thereof.

12. A process for the preparation of compounds of the general formula I substantially as described with reference to Example 1.

13. A process for the preparation of compounds of the general formula I substantially as described with reference to any one of Examples 6 to 8, 10 and 11.

14. A process for the preparation of compounds of the general formula IV substantially as described with reference to any one of Examples 2, 3 and 5.

15. A process for the preparation of compounds of the general formula IV substantially as described with reference to Example 4 or 9.

16. Compounds of the general formula I when prepared by the process claimed in any one of claims 1 to 5, 12 and 13.

17. Compounds of the general formula IV when prepared by the process claimed in any one of claims 6 to 10, 14 and 15.

ELKINGTON & FIFE,
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Bank Chambers, 329, High Holborn,
London, W.C.1,
Agents for the Applicants.

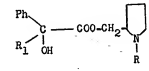
PROVISIONAL SPECIFICATION

Improvements in or relating to the preparation of Pyrrolidyl Esters and Quaternary Compounds thereof

We, BEECHAM RESEARCH LABORATORIES LIMITED, a British Company, of Brockham Park, Betchworth, Surrey, do hereby declare this invention to be described in the following statement:—

This invention relates to a process for the preparation of basic esters and quaternary compounds thereof.

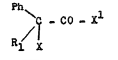
The present invention provides a process for the preparation of compounds of the general formula:



(I)

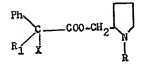
wherein a 1-alkyl-2-hydroxymethyl pyrrolidine of the general formula:

is reacted with an acid halide of the general formula:



(II)

where X and X^1 are each an atom of chlorine or bromine, R is an alkyl group having from 1 to 4 carbon atoms and R_1 is a phenyl or cyclohexyl group, to give a compound of the general formula:



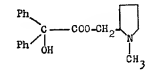
.HX (III)

and the compound of the general formula III is then converted into a compound of the general formula I by treatment with water and a base.

The abbreviation "Ph" is used herein for the phenyl group.

The compounds of the general formula III are new compounds.

The process of the present invention has been found to be particularly suitable for the preparation of compounds of the general formula I where the group R_1 is a phenyl group and especially where the group R is a methyl or ethyl group. Particularly satisfactory results have been obtained using the process of this invention in the preparation of the compound of the formula:



from 1-methyl-2-hydroxymethyl pyrrolidine and α-chlorodiphenylacetyl chloride as described in Example 1 below.

The treatment of the halogen compound of the general formula III with water according to the process of this invention can conveniently be achieved by allowing the halogen compound to stand in water. Where the halogen compound to be treated is (1-methyl-2-pyrrolidyl)methyl diphenylchloroacetate hydrochloride, it has been found that the corresponding hydroxy compound can be obtained very satisfactorily by dissolving the former compound in water and allowing the resulting solution to stand at room temperature for about 30 minutes.

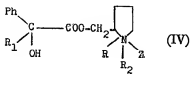
The treatment of compounds of the general formula III with water and with a base according to the process of this invention can, if desired, be carried out simultaneously by using an aqueous solution of the base. However, it is generally preferable to treat the compound of the general formula III first with water to obtain the corresponding hydroxy compound and then to treat the latter with the base. Suitable bases include aqueous solutions of alkalis, for example sodium hydroxide.

The first stage of the process of this invention in which a 1-alkyl-2-hydroxymethyl pyrrolidine is reacted with an acid halide can be carried out at any convenient temperature. In general this first stage can be performed by mixing the reactants and allowing the mixture to stand without the application of external heat. However, if it is wished to complete the reaction in the first stage more quickly the mixture of reactants can be heated.

The solvent used in the first stage of the reaction depends to some extent upon the temperature employed. Very satisfactory results have been obtained using butanone as solvent.

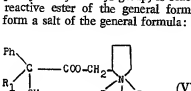
Compounds of the general formula I are valuable as intermediates in the preparation of the corresponding quaternary compounds which possess valuable properties as spasmolytics.

The present invention, therefore, includes a process for the preparation of quaternary compounds of the general formula:



(IV)

where R is an alkyl group having from 1 to 4 carbon atoms, R_1 is a phenyl or cyclohexyl group; R_2 is an alkyl group (especially an alkyl group having not more than 4 carbon atoms), or an aralkyl group (for example a benzyl group); and Z is a halogen, alkyl sulphate or aryl sulphonate radical, wherein a compound of the general formula I where R is an alkyl group having from 1 to 4 carbon atoms and R_2 is a phenyl or cyclohexyl group, is reacted with a reactive ester of the general formula R_2Z to form a salt of the general formula:



(V)

and then the anion Z^1 is exchanged for the anion Z in the event of the latter not being a halogen, alkyl sulphate or aryl sulphonate radical.

The anion of the compounds of this invention can be chosen from any of the usual accepted anions, for example halide, sulphate, citrate or tartrate, the choice depending to a large extent upon the pharmaceutical convenience and the physical properties which it is desired the salts to possess, for example a particular stability or solubility. Of course, toxic anions, for example the oxalate ion, should be avoided.

The exchange of the anion Z^1 for the anion Z referred to above can be achieved by treating the quaternary compound of the general formula V with the silver salt of the appropriate acid having the anion Z.

A number of the compounds included in the general formula I are new compounds which have not previously been described. Examples of these new compounds are:—

(a) the compound of formula I where R_1 and R are cyclohexyl and methyl groups respectively;

(b) the compound of formula I where R_1 and R are phenyl and *n*-butyl groups respectively.

The processes of this invention are equally applicable to optically active and optically inactive materials.

The following Examples illustrate the invention:

EXAMPLE 1.

This Example describes the preparation of (1-methyl-2-pyrrolidyl)methyl benzilate.

A solution of optically active 1-methyl-2-hydroxymethyl pyrrolidine (16 g.) in butanone (40 c.c.) was added in drops while stirring to a solution of α-chloro-diphenylacetyl chloride (39.2 g.) in butanone (80 c.c.) care being taken to keep the temperature during the addition below 35° C. The reaction mixture was allowed to stand overnight at 0° C. and after removal of the butanone *in vacuo* the (1-methyl-2-pyrrolidyl) methyl diphenyl-chloroacetate hydrochloride was refluxed with dry ether (2 × 120 c.c.) and then triturated with dry ether to give the crude hydrochloride (37 g).

A solution of the (1-methyl-2-pyrrolidyl)-methyl diphenylchlorocacetate hydrochloride (37 g.) in water (700 c.c.) was allowed to stand at room temperature for 25 minutes. Sodium chloride (250 g.) was added and the solution extracted with chloroform (6 × 100 c.c.). The chloroform extracts were dried using magnesium sulphate and the solvent removed *in vacuo* leaving a gum as the residue. The latter on crystallisation from a mixture of ethanol and ether yielded (1-methyl-2-pyrrolidyl)methyl benzilate hydrochloride (29 g.) as colourless needles, m.p. 170—171° C. (Found: C, 66.4; H, 6.7; N, 4.3; Cl, 9.9%. $C_{20}H_{24}O_3NCl$ requires C, 66.4; H, 6.6; N, 3.9; Cl, 9.8%).

Treatment of the hydrochloride (29 g.) dissolved in water with an aqueous solution of sodium hydroxide gave the ester base (24 g.) as colourless needles, m.p. 100—101° C. from petroleum ether (60—80° C.). (Found: C, 73.9; H, 7.2; N, 4.3%. $C_{20}H_{23}O_3N$ requires: C, 73.8; H, 7.1; N, 4.3%). $[\alpha]_D^{25}$=+4.9 (c=11, water).

The optically active 1-methyl-2-hydroxymethyl pyrrolidine used in the process described above was obtained as a colourless liquid, b.p. 57—58° C./4 mm. $n_D^{19.4}$ 1.4692 $[\alpha]_D^{21}$ = −33.6° by the formaldehyde-formic acid methylation of 2-hydroxymethyl pyrrolidine. The latter was prepared by the reduction of butyl pyroglutamate with lithium aluminium hydride (cf. Karrer and Portman, *Helv. Chem. Acta.*, 1948, *31*, 2088). It was obtained in 62% yield as a colourless optically active liquid, b.p. 89° C./6 mm. n_D^{25} 1.4846, $[\alpha]_D^{21}$=+1.8°.

EXAMPLE 2.

This Example describes the preparation of (1-methyl-2-pyrrolidyl)methyl benzilate methiodide.

(1-Methyl-2-pyrrolidyl)methyl benzilate (12.2 g.) obtained as described in Example 1 was dissolved in dry benzene (50 c.c.) and to the solution was added methyl iodide (7.5 c.c.). The reaction mixture became turbid and was

allowed to stand at room temperature for twenty hours, after which the benzene layer was decanted and the gum remaining was washed with dry ether, triturated with dry ethanol and allowed to stand overnight at 0° C. The product obtained was the crude methiodide (17 g.—yield 97%) which, after being crystallised from a mixture of ethyl acetate, methanol and ether, was obtained as colourless micro prisms, m.p. 192° C. (Found: C, 53.8; H, 5.7; I, 26.8%. $C_{23}H_{28}O_2NI$ requires: C, 54.0; H, 5.6; I, 27.2%).

EXAMPLE 3.

This Example describes the preparation of (1-methyl-2-pyrrolidyl)methyl benzilate ethiodide.

(1-Methyl-2-pyrrolidyl)methyl benzilate (2 g.) was treated with ethyl iodide (1.5 c.c.) in benzene (10 c.c.) using the method described in Example 2, to give the ethiodide (1.2 g.—yield 40%) which crystallised from a mixture of ethyl acetate, methanol and ether as colourless needles, m.p. 146—148° C. (Found: C, 54.7; H, 5.6; I, 26.0%. $C_{25}H_{32}O_2NI$ requires: C, 54.9; H, 5.8; I, 26.4%).

EXAMPLE 4.

This Example describes the preparation of (1-methyl-2-pyrrolidyl)methyl benzilate methyl metho-sulphate.

(1-Methyl-2-pyrrolidyl)methyl benzilate (20 g.) was dissolved in dry benzene (100 c.c.) and dimethyl sulphate (18 c.c.) was added. After refluxing for 10 minutes the reaction mixture was cooled and the colourless solid (23 g.—yield 84%) that separated was removed by filtration. This solid was crystallised several times from a mixture of butanone, ethanol and ether after which (*1-methyl-2-pyrrolidyl*)-*methyl benzilate methyl metho-sulphate* was obtained as colourless needles, m.p. 152—153° C. (Found: C, 58.9; H, 6.5; S, 6.9%. $C_{25}H_{29}O_5NS$ requires: C, 58.5; H, 6.4; S, 7.1%).

The (1-methyl-2-pyrrolidyl)methyl benzilate used in the preparation described above was the optically active form prepared as described in Example 1.

EXAMPLE 5.

This Example describes the preparation of (1-methyl-2-pyrrolidyl)methyl benzilate methyl metho-sulphate from optically inactive (1-methyl-2-pyrrolidyl)methyl benzilate.

(1-Methyl-2-pyrrolidyl)methyl benzilate (325 g.) was dissolved in warm dry acetone (1200 c.c.) and dimethyl sulphate (158 g.) was added. After the initial exothermic reaction was complete the mixture was refluxed for 15 minutes and then cooled. The precipitated (1-methyl-2-pyrrolidyl)methyl benzilate methyl metho-sulphate obtained (384 g.—yield 85%), m.p. 135—137° C. was removed by filtration and could be recrystallised from a mixture of 10% ethanol in butanone.

The (1-methyl-2-pyrrolidyl)methyl benzilate used in the preparation described in this Example was optically inactive and had been prepared from optically inactive 1-methyl-2-hydroxymethyl pyrrolidine obtained as described in our Specification No. 21193/56 (Serial No. 820,503).

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